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Scoccianti, Chiara; Key, Timothy J.; Anderson, Annie S.; Armaroli, Paola; Berrino, Franco; Cecchini, Michele

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European Code against Cancer 4th Edition: Breastfeeding and cancer[☆]

Chiara Scoccianti^a, Timothy J. Key^b, Annie S. Anderson^c, Paola Armaroli^d, Franco Berrino^e, Michele Cecchini^{f,1}, Marie-Christine Boutron-Ruault^g, Michael Leitzmann^h, Teresa Noratⁱ, Hilary Powers^j, Joachim Schüz^a, Martin Wiseman^m, Isabelle Romieu^{a,*}

^a International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France

^b Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, United Kingdom

^c Centre for Research into Cancer Prevention & Screening, Level 7, Mailbox 7, Ninewells Hospital & Medical School, Dundee, DD1 9SY, Scotland, United Kingdom

^d CPO Piemonte, AO Città della Salute e della Scienza di Torino, Turin, Italy

^e Fondazione IRCSS Istituto Nazionale dei Tumori, 1 via Venezian, 20133 Milan, Italy

^f Health Policy Analyst OECD, 2 rue André Pascal, 75775, Paris Cedex 16, France

^g Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France

^h Department of Epidemiology and Preventive Medicine, University of Regensburg, 93042 Regensburg, Germany

ⁱ Department of Epidemiology and Biostatistics, School of Public Health Imperial College London, St Mary's Campus, London W2 1PG, United Kingdom

^j Human Nutrition Unit, The Medical School, Beech Hill Road, Sheffield S10 2RX, United Kingdom

^m World Cancer Research Fund International, Second Floor, 22 Bedford Square, London WC1B 3HH, United Kingdom

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ABSTRACT

Breast cancer is the most frequent cancer in women, and incidence rates have been rising in European Union (EU) countries over recent decades due in part to a sharp decline in breastfeeding practices. Evidence for a protective association between breastfeeding and the risk of breast cancer at all ages is convincing, and modest protective relationships between breastfeeding and the risk of endometrial and ovarian cancers have been suggested. The reduction in breast cancer risk is estimated at 2% for an increase of 5 months of lifetime breastfeeding. The longer women breastfeed, the more they are protected against breast cancer. In addition, breastfeeding is associated with several health benefits for both the mother and the breastfed child. Taking all this evidence into account, the 4th edition of the European Code against Cancer recommends: "Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby".

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Abbreviations: IARC, International Agency for Research on Cancer; WHO, World Health Organisation; EU, European Union; RR, Relative Risk.

* Corresponding author at: IARC European Code Against Cancer Secretariat, 150 Cours Albert Thomas, F-69372 Lyon Cedex 08, France. Tel.: +33 04 72 73 84 85.

E-mail address: secretariat-cancer-code-europe@iarc.fr (I. Romieu).

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1. Introduction

Breast cancer is the most frequent cancer in women; it shows growing incidence rates together with a levelling towards decreased mortality across European Union (EU) countries. The increasing incidence over subsequent generations is also related to the increased prevalence of breast cancer risk factors such as later age at first pregnancy, decreased parity and breastfeeding. Breastfeeding for at least 5–6 months has a protective effect on the risk of developing breast cancer and possibly endometrial and ovarian cancers [1]. Breastfeeding is also associated with a more rapid return to pre-pregnancy weight and lower incidence of the metabolic syndrome for the mother, and with lower incidence

Box 1. European Code Against Cancer.

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

1. Do not smoke. Do not use any form of tobacco
2. Make your home smoke free. Support smoke-free policies in your workplace
3. Take action to be a healthy body weight
4. Be physically active in everyday life. Limit the time you spend sitting
5. Have a healthy diet:
 - Eat plenty of whole grains, pulses, vegetables and fruits
 - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks
 - Avoid processed meat; limit red meat and foods high in salt
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions
9. Find out if you are exposed to radiation from naturally high radon levels in your home; take action to reduce high radon levels
10. For women:
 - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby
 - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT
11. Ensure your children take part in vaccination programmes for:
 - Hepatitis B (for newborns)
 - Human papillomavirus (HPV) (for girls)
12. Take part in organised cancer screening programmes for:
 - Bowel cancer (men and women)
 - Breast cancer (women)
 - Cervical cancer (women)

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

of respiratory tract infections and later obesity for the breastfed infant [2,3]. Taken together, the 4th edition of the European Code Against Cancer (Box 1) [4] advocates action-oriented recommendations for the general public. The Code recommends breastfeeding babies in order to decrease the risk of breast cancer and to gain several short- and long-term health benefits.

1.1. Breastfeeding trends in Europe

The World Health Organisation (WHO) has developed a common set of breastfeeding definitions to help standardise the assessment of breastfeeding practices in the global context [5]. The WHO defines *ever breastfeeding* as the baby having *ever* been put to the breast, even if only once, and *exclusive breastfeeding* as the baby having received *only* breast milk during a specific period of time. Yet defining breastfeeding rates on the basis of WHO indicators remains challenging, and methods of breastfeeding data collection vary greatly between countries (Fig. 1) [6–8]. In European countries, where data are available, rates of *ever* breastfeeding at age 3 months range from 22.7% to 97.6%, while averages are lower and range from 16% to 96.5% by the time infants are 6 months old [8,9]. EU breastfeeding data on infants *exclusively* breastfed for the first 6 months of life place Germany as having the developed world's highest known breastfeeding rates (22%), according to the WHO standard; Finland, Ireland, Switzerland and Austria in the higher breastfeeding category (15%, 15%, 14%, and 10%, respectively); and France, Scotland and Belgium ($\leq 1\%$) as having far lower rates than the other EU countries [10]. Overall, the incidence of exclusive breastfeeding and its duration tend to be higher in countries that support long maternity/parental leave, such as Germany, the Nordic

countries, Hungary and the Czech Republic. Other determinants of the breastfeeding practice include infant characteristics and societal and cultural norms of the feeding choice [11].

A 'Global Strategy for Infant and Young Child Feeding' is endorsed by the WHO member states and the United Nations Children's Fund (UNICEF) Executive Board [12]. However, breastfeeding rates and practices in EU countries fall short of WHO/UNICEF recommendations, and different areas need implementation, including public health policy, legislation formulation, adoption of the WHO code of breast-milk substitutes, marketing issues, and information on infant feeding. Adequate information, education and communication are crucial to promote, protect and support breastfeeding in countries where formula feeding (food substitutes used to replace breastfeeding) has been considered the norm for several years/generations.

1.2. Breast cancer incidence in Europe

Breast cancer (International Classification of Diseases: C-50) [13] is the second most common cancer in the world and by far the most frequent cancer in women, with an estimated 1.67 million new cancer cases (representing 25% of all cancers) diagnosed in 2012 [14]. The International Agency for Research on Cancer (IARC), in collaboration with the European Network of Cancer Registries [15], provides estimates of the EU cancer burden from 25 years ago [16,17]. Breast cancer incidence is strongly related to age, and European rates rise steeply from around age 30–39 until the menopause, when the increase slows down or remains stable, subsequently increasing to reach an overall peak in the 80+ age group [17]. In 2012, breast cancer was the leading cancer in women in all EU countries, with an estimated 500,000 (28.6%) new breast cancer cases distributed in a clear geographic pattern (Fig. 2). Incidence rates vary nearly three-fold across EU regions and attain nearly 96 per 100,000 population in Western Europe. Higher incidence rates are estimated in Belgium (147), Denmark (143) and France (137), followed by Iceland (131), the United Kingdom (129) and Finland (121). In comparison, incidence rates in Eastern European countries such as the Ukraine and Moldova are much lower (54 and 53, respectively) [17]. This variability may reflect the extent and type of mammographic screening activities, as well as a variance in the prevalence and distribution of known breast cancer risk factors (e.g. family history, reproductive factors, consumption of alcoholic beverages [1,18]) across European countries.

UNICEF estimates that an increase of 16% in the proportion of women who breastfeed for 6 months could lead to 1.6% of expected breast cancer cases being avoided each year. The scenario with the greatest benefit (2.9% of breast cancer cases avoided) would follow if the number of women who never breastfed were to be halved and the breastfeeding rates for 18+ months were doubled [19].

2. Association with cancer

There is abundant epidemiological evidence from both cohort and case-control studies that a longer duration of breastfeeding is linearly correlated with a lower risk of both premenopausal and postmenopausal breast cancer [1,20], in addition to a modest protective association with risk of endometrial and ovarian cancers. To estimate the long-term effects of breastfeeding on the risk of cancer, we report on studies which compared women who breastfed for less than a given number of months to those who breastfed for longer periods; those studies comparing ever- to never-breastfeeding will tend to underestimate any association.

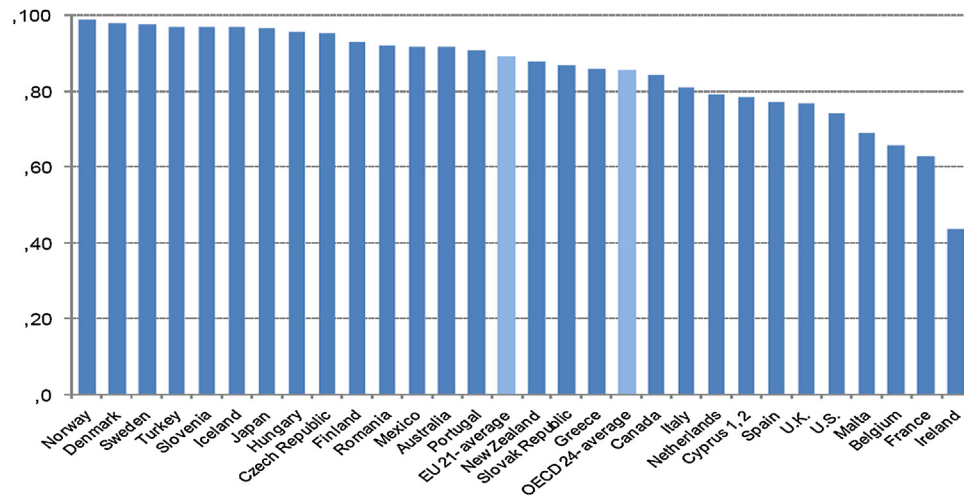


Fig. 1. Proportion of ever-breastfed children (proportion of children who were breastfed at least once) around 2005. Data were collected between 2000 and 2007 by national surveys. Around 2005, the proportion of children who were ever-breastfed varied widely across EU countries.
Source: OECD (2014), [8].

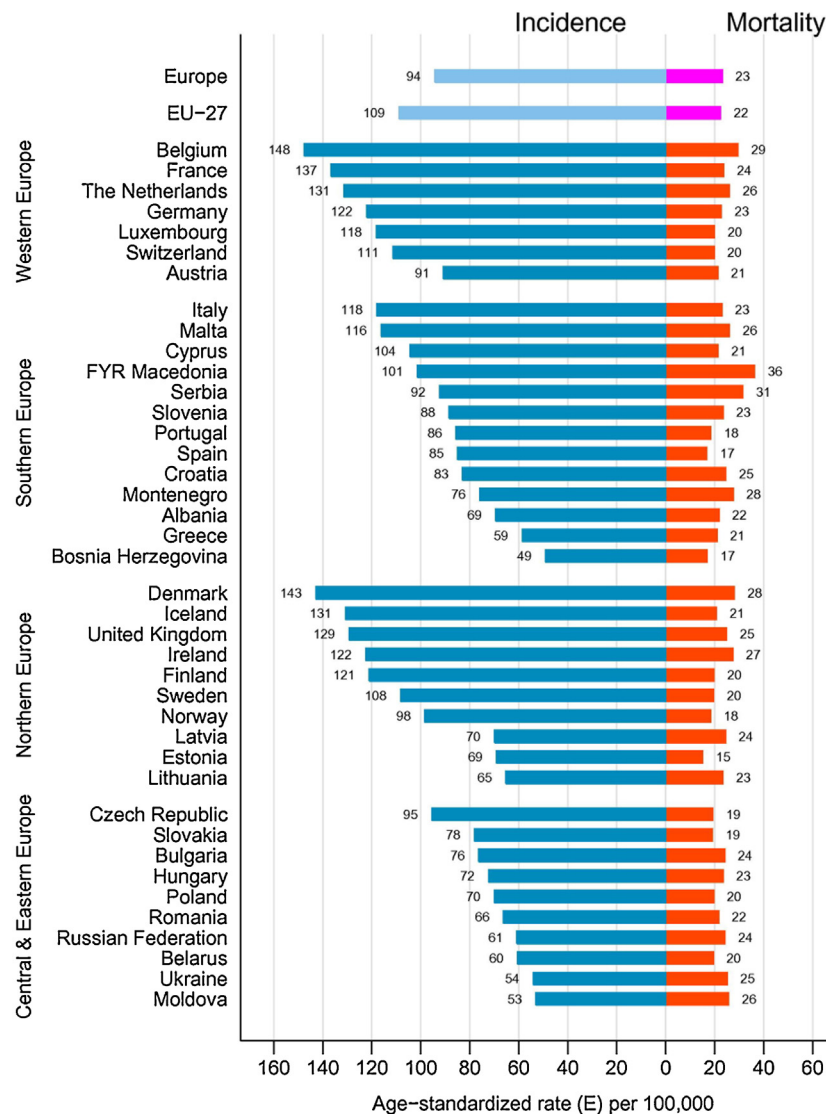


Fig. 2. Age-standardised breast cancer incidence and mortality rates by area and country in Europe 2012. The figure shows a three-fold variation with a clear geographical pattern; the high mortality rates in the northern countries reflect the high incidence, while in the south there is a high mortality-to-incidence ratio, a proxy of unfavourable survival.

Source: from Ferlay et al. [17]. Copyright Elsevier (2013).

2.1. Cancer risk by total duration of breastfeeding

Breast cancer risk is strongly related to several reproductive and hormonal factors at once [21,22]; determining the effects of breastfeeding independently of those of child-bearing will require several studies with great power analysis. Early research showed that a first full-term pregnancy at a young age reduces the risk of breast cancer later in life, and suggested that the observed protective effect was due largely to the mother's age rather than to the number of her pregnancies [21]. Subsequent research showed that each additional birth (and associated breastfeeding period) occurring before the age of 30 contributed to a reduction in the risk of breast cancer [23]. Research by the international Collaborative Group on Hormonal Factors in Breast Cancer – based on individual data from over 50,000 women with breast cancer in 30 different countries – has shown that breastfeeding has a protective effect estimated at a 4.3% risk reduction for every 12 months of cumulative breastfeeding (in addition to an estimated 7.0% reduction in risk for each birth) (Fig. 3) [20]. The same study showed that breast cancer risk was reduced in both premenopausal and postmenopausal women, with no significant difference in the effect estimated according to menopausal status. The meta-analysis performed by the Continuous Update Project of the World Cancer Research Fund estimated the decreased breast cancer risk at 2% (pooled OR = 0.98; 95% CI: 0.97–0.98) for an increase of 5 months of total breastfeeding [1]. Relatively few studies have made the distinction between exclusive breastfeeding and mixed feeding, or observed the effects on different hormonal breast-cancer subtypes. Results published so far suggest that exclusive breastfeeding may reduce the risk of both oestrogen-receptor-positive and oestrogen-receptor-negative breast cancers [24].

Available evidence suggests that a long duration of breastfeeding may also have a modest protective effect on the risk of endometrial and ovarian cancers [25,26]. A recent meta-analysis suggested that the RR of epithelial ovarian cancer is significantly decreased (by 8%; summary RR = 0.92; 95% CI: 0.90–0.95) for each 5-month increase in total breastfeeding duration [27]. Overall, at present the evidence suggesting that breastfeeding protects against ovarian cancer is limited, and too limited to draw definite conclusions on the effect of lactation on endometrial cancer risk [28,29].

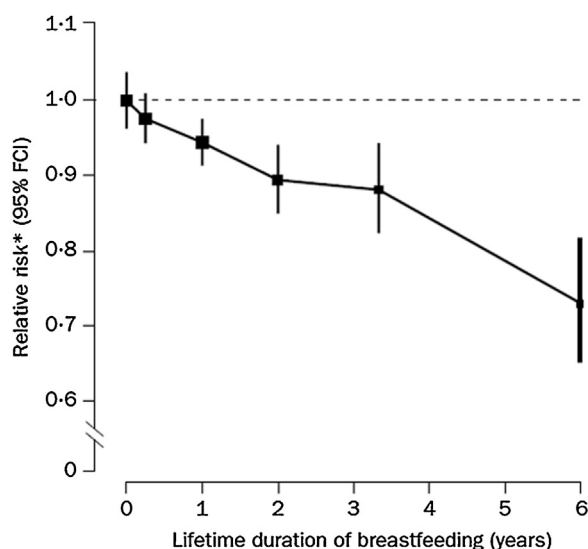


Fig. 3. Risk of breast cancer in relation to lifetime duration of breastfeeding. Relative risk (calculated as floating absolute risk) of breast cancer in parous women adjusted for parity, age, age at first birth, and menopausal status.

Source: Collaborative Group on Hormonal Factors in Breast Cancer [20].

2.2. Biological plausibility

Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts, and connective tissue. The breast organ develops in response to hormones such as oestrogens, progesterone, insulin and growth factors, and hormone dependency *per se* is a well-known and important characteristic of breast cancer [30]. The main periods of development are during puberty, pregnancy and lactation, while the glandular tissue atrophies after menopause. Different reproductive factors – such as breastfeeding, pregnancy-related interruption of ovulation and post-weaning breast remodelling – all involve changes in lifetime exposure to oestrogen and to other hormones and permanently alter the breast molecular histology.

Human data suggest that hormonal mechanisms are involved in pregnancy-related protection against breast cancer, and there is substantial evidence that pregnancy causes differentiation of the breast epithelium which makes the cells less susceptible to malignant transformation. Also, it has been suggested that long-term hormonal changes occur after pregnancy and may contribute to lower the risk [31–33].

In addition to the impact of pregnancy, prolonged breastfeeding may lower the periodic influence of oestrogen/progesterone on breast tissue and thus protect against breast cancer. Breastfeeding postpones the resumption of ovulatory menstrual cycles after a pregnancy, reduces oestrogen levels in the breast, and fully differentiates breast tissue, making it less susceptible to the hormonal milieu [34–36]. After delivery, circulating oestrogen and progesterone levels fall dramatically, which allows cortisol binding to occur and lactogenesis to proceed [37].

The strong exfoliation of breast tissue during lactation and the massive epithelial apoptosis at the end of breastfeeding could also contribute to decreasing the risk of cancer by excreting cells with initial DNA damage from the breast ductal tissue [25,38]. Mouse models show that breast carcinogenesis is significantly inhibited after a full-term pregnancy, probably a result of permanent structural and functional changes induced in the mammary parenchyma by the reproductive process, resulting in a lower susceptibility of epithelial cells to future carcinogenic stimuli [39].

3. Justification for recommendation

Breastfeeding protects against the risk of developing both premenopausal and postmenopausal female breast cancer and possibly also endometrial and ovarian cancers. In addition, lactation is associated with several health benefits for the mother and the breastfed child.

3.1. Additional health benefits for the mother

Observational studies show that breastfeeding may favour the return to pre-pregnancy weight and metabolic profile [40–43]. It appears that the metabolic load of exclusive breastfeeding (about 500 kcal per day) may help in losing the weight gained during pregnancy. Overall, less than 1 kg weight change from pre-pregnancy or first trimester to 1–2 years postpartum is observed in mothers who breastfeed [40]. In the UK Million Women Study, Bobrow et al. reported that at every parity level the mean standardised body mass index was significantly lower among women (mean age 57.4 years) who had previously breastfed, decreasing 0.22 kg/m² for every 6 months of breastfeeding [44]. In addition to the benefits on body weight, data from the North American CARDIA study [42] have demonstrated that longer duration of lactation is associated with lower incidence of the metabolic syndrome many years after weaning.

3.2. Health benefits for the breastfed infant

The WHO recommends 6 months as the optimal duration of exclusive breastfeeding on the basis of strong evidence of both short- and long-term benefits for the infant [45]. Breastfeeding provides all the nutrients infants need and prevents a substantial proportion of hospital admissions due to diarrhoea and lower respiratory tract infection in early childhood [2]. Breastfeeding affects not only the incidence but also the severity of these infections in low-, middle-, and high-income countries [46]. The protection against infections is due to several antimicrobial and anti-inflammatory factors, as well as hormones, digestive enzymes, and growth and immune modulators contained in breast milk [47–49]. Later in life, having been breastfed has a beneficial association with blood pressure, type-2 diabetes and serum cholesterol [3]. Infants who are breastfed appear to have a reduced risk of obesity in childhood and adolescence compared to those who are formula-fed, but overall results are still inconsistent [50,51]. The mechanisms by which breastfeeding may impact on later weight development have not been clearly identified [52]. However, a lower protein intake and higher energy metabolism [53] and a lower insulin response (resulting in a decreased number of adipocytes compared to formula-fed infants [54]) are likely to be involved. Meta-analyses show that breastfeeding is inversely related to some cancers of the mothers' offspring, significantly so for acute lymphoblastic leukaemia, Hodgkin's disease, and neuroblastoma. At present it is yet unclear whether the observed small reduction in risk is a generalised effect of breastfeeding or whether it reflects some common bias due to self-reported information in most of the case-control studies that have examined this question [55].

Taking all this evidence into account, the European Code Against Cancer has developed the following recommendation:

"Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby."

4. Conclusion

Breast cancer is the most frequent cancer in women in all EU countries; hence the potential for primary prevention is substantial. Convincing epidemiological evidence together with several plausible biological mechanisms support the conclusion that prolonged cumulative periods of breastfeeding are protective against the development of breast cancer, and possibly also endometrial and ovarian cancers. The longer a woman breastfeeds, the more she is protected against breast cancer. The most conclusive finding about the protective effect of breastfeeding on risk of breast cancer derives from studies where women have long durations of cumulative breastfeeding. Breast cancer risk is reduced by about 4% for every cumulative 12 months of breastfeeding, in addition to a risk reduction due directly to having had a baby [20]. A lower breast cancer risk of approximately 2% can be achieved by exclusively breastfeeding for at least 6 months [1,20]. Public health policies aimed at supporting breastfeeding will improve the quality of life for women by reducing cancer incidence and for children by reducing acute and chronic diseases. In conclusion, it is important to carefully consider all necessary measures to promote prolonged breastfeeding at the EU level for the health of both mother and baby.

The resulting recommendation of the 4th edition of the European Code Against Cancer targeted at women is to breastfeed their baby for prolonged periods, if they have the choice, as it will lead to a reduction in their risk of getting breast cancer.

Conflict of interest

The authors declare no conflict of interest.

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